CARDIOVASCULAR DRUGS - Blood Lipid Affecting Drugs (Matthias Hollmann, Hans Dieter Lehmann, Hans P. Albrecht, Marco Thyes)

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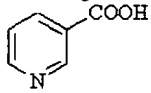
4.3. Drugs Affecting Lipoprotein Synthesis

4.3.1. Nicotinic Acid and Derivatives

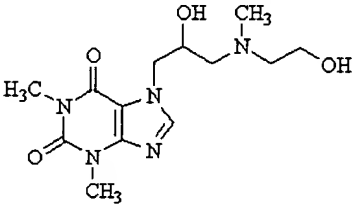
Nicotinic acid decreases the rate of synthesis of VLDL and LDL, increases LDL catabolism, and inhibits lipolysis. It is effective in type II to type V hyperlipoproteinemias. To minimize such side effects as flush or pruritus and to prolong the duration of action prodrugs and timed-release formulations have been developed. A new analog with significant advantages is acipimox which is effective at lower doses than nicotinic acid and encumbered with fewer side effects [50].

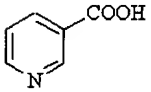
Nicotinic acid [*59-67-6*], pyridine-3-carboxylic acid, $C_6H_5NO_2$, M_r 123.11, *mp* 236.6 °C, is synthesized by the reaction of paraldehyde with ammonia to form 5-ethyl-2-methylpyridine [51] and subsequent oxidation with nitric acid [52], see also → Pyridine and Pyridine Derivatives.



Trade names: Niacin (numerous suppliers), Nicobid, Nicolar (both Rhône-Poulenc Rorer).

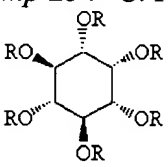
Xantinol nicotinate [*437-74-1*], pyridine-3-carboxylic acid and 3,7-dihydro-7-[2-hydroxy-3-[(2-hydroxyethyl)-methylamino]propyl]-1,3-dimethyl-1-*H*-purine-2,6-dion (1 : 1), $C_{19}H_{26}N_6O_6$, M_r 434.35, *mp* 180 °C. Preparation according to [53].

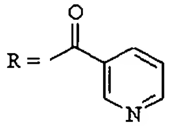




Trade name: Complamin (Smith Kline Beecham).

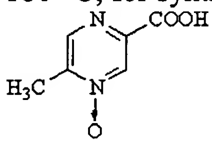
Inositol nicotinate [*6556-11-2*], myo-inositol hexa-3-pyridinecarboxylate, $C_{42}H_{30}N_6O_{12}$, M_r 810.73, *mp* 254 °C. For synthesis see [54].





Trade names: Hexanicit (Astra), Nicolip (Henning).

Acipimox [*51037-30-0*], 2-carboxy-5-methylpyrazine 4-oxide, $C_6H_6N_2O_3$, M_r 154.13, *mp* 177 – 180 °C; for synthesis see [55].



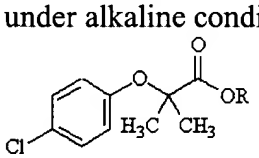
Trade names: Olbemox (Farmitalia Carlo Erba, Pharmacia-Upjohn), Olbetam (Farmitalia Carlo Erba).

4.3.2. Aryloxyisobutyric Acids, Derivatives, and Analogs

The class of compounds treated in this section comprises numerous substances with similar chemical, pharmacological, and clinical properties, which act primarily as antihypertriglyceridemic agents. The decrease in cholesterol levels is only moderate; therefore, these drugs are used mainly in type IIb, III, and type IV hyperlipoproteinemias. The oldest and still most widely used representative is clofibrate [56], which has been on the market since 1963. Mechanism of action of the fibrates is not yet completely understood. They increase the rate of VLDL catabolism by stimulating lipoprotein lipase activity and/or hepatic lipase activity [57], thereby lowering mainly plasma triglycerides. Other effects are inhibition of cholesterol synthesis and increase in excretion of neutral sterols [58].

Etofibrate combines the structural elements of nicotinic acid and clofibrate; therefore, it is used in all types of hyperlipidemias. The clofibrate analogs procetofene, bezafibrate, and gemfibrozil have only a small influence on the total cholesterol level, but they have been reported to lower selectively the LDL cholesterol level [25], [44], [59].

Clofibrate [*637-07-0*], 2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester, $C_{12}H_{15}ClO_3$, M_r 242.71, bp_{20} 148 – 150 °C, is synthesized by reaction of 4-chlorophenol with acetone and chloroform under alkaline conditions to form clofibric acid and subsequent esterification [60][61][62].

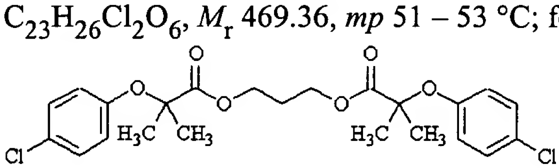


R = H: clofibric acid

R = C_2H_5: clofibrate

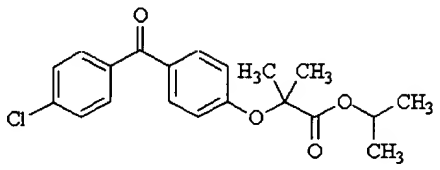
Trade names: Atromid (American Home Products, Zeneca), Regelan (Zeneca).

Simfibrate [*14929-11-4*], 2-(4-chlorophenoxy)-2-methylpropanoic acid 1,3-propanediyl ester, $C_{23}H_{26}Cl_2O_6$, M_r 469.36, *mp* 51 – 53 °C; for synthesis see [63].



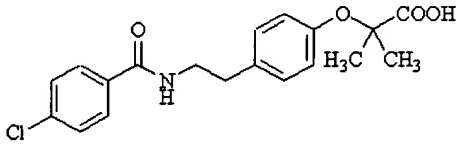
Trade name: Cholesolvin (Yoshitomi).

Procetofene [*49562-28-9*], fenofibrate, 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid 1-methylethyl ester, $C_{20}H_{21}ClO_4$, M_r 360.84, *mp* 80 – 81 °C; for synthesis, see [64].



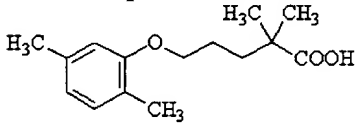
Trade name: Lipantyl (Fournier).

Bezafibrate [*41859-67-0*], 2-[4-[2-[(4-chloro-benzoyl)amino]ethyl]phenoxy]-2-methylpropanoic acid, $C_{19}H_{20}ClNO_4$, M_r 361.83, *mp* 155 – 156 °C; for synthesis, see [65].



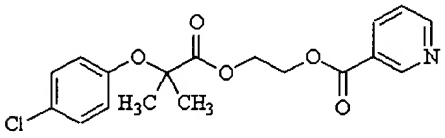
Trade name: Cedur (Roche).

Gemfibrozil [*25812-30-0*], 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, $C_{15}H_{22}O_3$, M_r 250.35, *mp* 61 – 63 °C; for synthesis, see [66], [67].



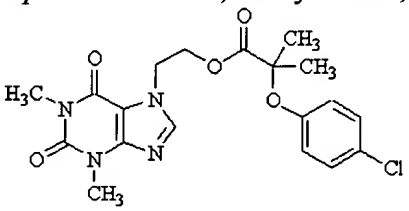
Trade names: Gevilon, Lopid (both Warner-Lambert).

Etofibrate [*31637-97-5*] , 2-hydroxyethyl nicotinate 2-(4-chlorophenoxy)-2-methylpropionate (ester), $C_{18}H_{18}ClNO_5$, M_r 363.79, *mp* 100 °C; for synthesis, see [68].



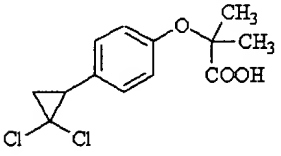
Trade name: Lipo-Merz (Merz).

Etofyllin clofibrate [*54504-70-0*], theofibrate, 2-(4-chlorophenoxy)-2-methylpropanoic acid 2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7*H*-purin-7-yl) ethyl ester, $C_{19}H_{21}ClN_4O_5$, M_r 420.85, *mp* 133 – 135 °C; for synthesis, see [69].



Trade name: Duolip (Mepha, Merckle).

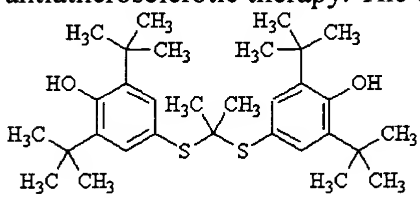
Ciprofibrate [*52214-84-3*], 2-[4-(2,2-dichlorocyclopropyl) phenoxy]-2-methyl-propanoic acid, $C_{13}H_{14}Cl_2O_3$, M_r 289.16, *mp* 114 – 116 °C; for synthesis, see [70].



Trade name: Lipanor (Sanofi).

4.3.3. Probucol

Probucol [*23288-49-5*], 4,4′-[(1-methylethylidene)bis(thio)]bis[2,6-bis(1,1-dimethylethyl)phenol], $C_{31}H_{48}O_2S_2$, M_r 516.84, *mp* 125 – 127 °C, lowers cholesterol by an as yet only partially elucidated mechanism, which involves inhibition of cholesterol synthesis and increase in the elimination of bile acids. Probucol decreases LDL and it has been reported also to have an antioxidative effect on LDL which may retard atherosclerotic progression [71]. In addition to decreasing LDL levels, probucol also lowers HDL cholesterol levels. This fact may require a careful evaluation of its usefulness in antiatherosclerotic therapy. The oral absorption of probucol is low (5 – 10 %). For synthesis, see [72].

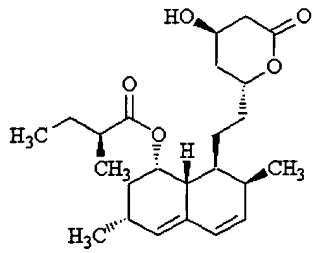


Trade names: Lorelco, Lurselle (both Hoechst Marion Roussel).

4.3.4. HMG-CoA Reductase Inhibitors

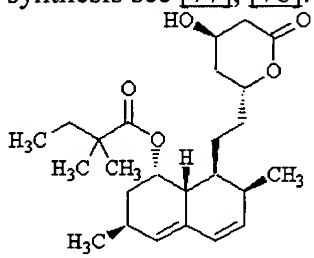
(CSE, Inhibitors, Statins). Compactin [73], [74] and mevinolin [75] are fungal metabolites isolated from the culture broths of *Penicillium citrinum* and *Aspergillus terreus,* respectively. Both compounds lower plasma cholesterol levels. They act by inhibiting β-hydroxy-β-methyl-glutaryl (HMG)-CoA-reductase, an enzyme that catalyzes an early rate-limiting step in cholesterol biosynthesis, i.e., reduction of HMG-CoA to mevalonic acid — the key substance for cholesterol biosynthesis. Following the demonstration of blood cholesterol reduction by this mechanism in humans [85], [86] intensive research and development led to introduction of lovastatin into therapy as the first drug of this class (1989). Since then, five additional compounds have been introduced, i.e., simva-, prava-, fluva-, atorva- and cerivastatin. Showing similar mechanism of action, these compounds differ in kinetics and metabolism (bioavailability < 5 to 60 %). The most active compound so far is cerivastatin with effective daily dosages below 1 mg compared to 10 – 160 mg for the other compounds. The considerable medical and market success of the statins as the most widely used lipid lowering drugs is based not only on the intrinsic properties of these compounds. All statins have to a considerable extent contributed to the increase in knowledge regarding pathophysiology, clinic features and therapy of lipid disorders by producing more or less extended and well designed clinical trials for therapy and prevention in a wide area of indications: primary and secondary hyperlipoproteinemias, primary and secondary prevention, coronary heart disease, stroke, etc., with highly differentiated subgroups. Important studies are listed as follows: MARS = Monitored Atherosclerosis Regression Study (lovastatin) [28], 4S = Scandinavian Simvastatin Survival Study [27], WOS = West of Scotland Study (pravastatin) [26], CARE = Cholesterol and Recurrent Events Trial (pravastatin) [29], FLUENT = Fluvastatin Long-Term Extension Trial [30], AVERT = Atorvastin Versus Revascularization Treatments (1999, in progress).

Lovastatin [*75330-75-5*], (2*S*)-2-methylbutanoic acid (1*S*, 3*R*, 7*S*, 8*S*, 8*aR*)-1,2,3,7,8,8*a*-hexahydro-3,7-dimethyl-8-[2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]-e ester, $C_{24}H_{36}O_5$, M_r 404.55, *mp* 174.5 °C. Lovastatin has been discovered and isolated as metabolite of *Monascus ruber.* [76] and from *Aspergillus terreus* [75].



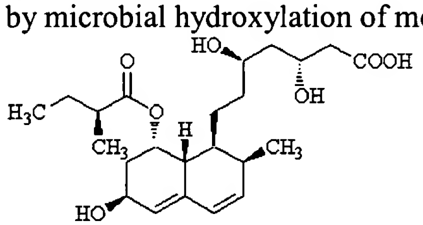
Trade names: Mevacor, Mevinacor (both Merck & Co.).

Simvastatin [*79902-63-9*], 2,2-dimethylbutanoic acid (1*S*, 3*R*, 7*S*, 8*S*, 8*aR*)-1,2,3,7,8,8*a*-hexahydro-3,7-dimethyl-8-[2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]-e ester, $C_{25}H_{38}O_5$, M_r 418.57, *mp* 135 – 138 °C. Simvastatin is a once-daily analogue of lovastatin. For synthesis see [77], [78].



Trade names: Denan (Boehringer Ingelheim), Lodales (Sanofi), Zocor (Dieckmann, Merck & Co).

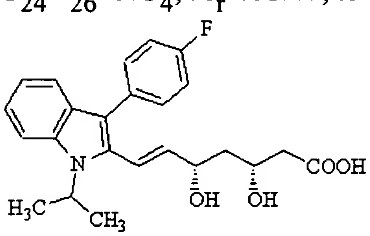
Pravastatin [*81093-37-0*], (β*R*,δ*R*,1*S*,2*S*,6*S*,8*aR*)-1,2,6,7,8,8*a*-hexahydro-β,δ,6-trihydroxy-2-methyl-8-[(2*S*)-2-methyl-1-oxobutoxy]· acid, $C_{23}H_{36}O_7$, M_r 424.53. Pravastatin is the bioactive metabolite of mevastatin. For its preparation by microbial hydroxylation of mevastatin [79] at the 6-position see [80].



Sodium salt [*81131-70-6*], $C_{23}H_{35}O_7Na$, M_r 446.52.

Trade names (sodium salt): Pravachol, Pravasin (both Bristol-Myers Squibb), Mevalotin (Sankyo).

Fluvastatin [*93957-54-1*], (3*R*,5*S*,6*E*)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, $C_{24}H_{26}FNO_4$, M_r 411.47, is a synthetic HMG-CoA reductase inhibitor, prepared according to [81].

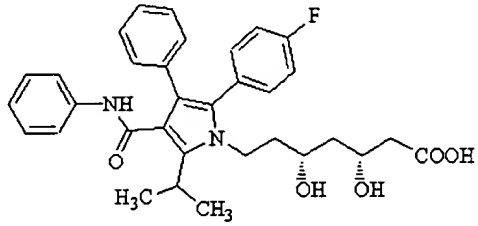


Sodium salt [*93957-55-2*], $C_{24}H_{26}FNaNO_4$, M_r 434.46, *mp* 194 – 197 °C.

Trade names (sodium salt): Canef, Cranoc (both Astra), Lescol (Novartis), Lochol (Tanabe Seiyaku).

Atorvastatin [*134523-00-5*], (β*R*,δ*R*)-2-(4-fluorphenyl)-β,

δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid, $C_{33}H_{35}FN_2O_5$, M_r 558.65. For synthesis see [82].

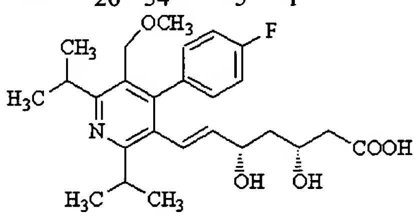


Calcium salt [*134523-03-8*], (β*R*,δ*R*)-2-(4-fluorphenyl)-β,
δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt, $C_{66}H_{68}CaFN_4O_{10}$, M_r 1155.38.

Atorvastatin calcium is the only HMG-CoA reductase inhibitor approved for type III and IV lipid disorders.

Trade names (calcium salt): Lipitor (Warner-Lambert, Pfizer), Sortis (Warner-Lambert).

Cerivastatin [*145599-86-6*],
(3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-5-methoxymethyl)-2,6-bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy acid, $C_{26}H_{34}FNO_5$, M_r 459.55. For synthesis see [83].



Sodium salt [*143201-11-0*], $C_{26}H_{33}FNaO_5$, M_r 481.54. Preparation of the sodium salt [84].

Trade names (sodium salt): Baycol (Bayer, Smith Kline Beecham), Lipobay (Bayer), Zenas (Fournier).

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